

Botulism

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Botulism is a rare, naturally occurring disease that can also be caused by accidental or deliberate exposure to botulinum toxins. *Clostridium botulinum* (*C. botulinum*) is a gram stain positive anaerobic organism and forms spores that can be found in soil, dust and aquatic sediments. Under suitable conditions, serologically distinct neurotoxins may be produced (A to G). Almost all human cases are caused by the A, B or E serotype; types C, D and E cause disease in mammals, birds and fish. These toxins are highly toxic and as little as 100 ng can be lethal.

There are three naturally occurring forms of illness: (i) food-borne botulism, caused by ingestion of pre-formed toxin; (ii) wound botulism, caused by growth of the bacterium and production of toxin in traumatic wounds; and (iii) intestinal colonization botulism, usually seen in infants (rarely in adults) caused by growth of bacterial cells and production of toxin in the gut. In addition, two other forms of botulism are recognized: (i) deliberate release of botulinum toxin, i.e. its use as a bio-weapon; and (ii) accidental botulism as a result of the therapeutic use of botulinum toxin. Cases of inhalational botulism have been reported in individuals purifying the toxin.

The neurological signs and symptoms of botulism are the same regardless of the type. The neurotoxins penetrate cells via a four-stage mechanism involving: (i) binding; (ii) internalization; (iii) membrane translocation; and (iv) target modification.¹ Botulinum toxin is a 150 kDa molecule that is comprised of a heavy chain (100 kDa) and a light chain (50 kDa) held together by a disulphide bond. The light chain contains endopeptidase enzyme which cleaves docking proteins called SNARE proteins. SNARE proteins enable vesicles containing acetylcholine to fuse with the presynaptic membrane to release acetylcholine into the synaptic cleft. Thus, the release of acetylcholine is prevented resulting in flaccid paralysis. The neurotoxin binds very tightly to the presynaptic nerve-ends of cholinergic nerves, so recovery is slow, occurring when new terminals have sprouted from the original nerve end-plate.

Epidemiology

Food-borne botulism

The term *botulus* is derived from the Latin word for 'sausage'. An outbreak of clostridial 'sausage poisoning' in Europe in the late 1700s was responsible for many deaths. Food-borne botulism is rare in the UK. It usually follows ingestion of home preserved meat, fish or vegetables and is more common in Southern and Eastern Europe where home food preservation is more popular.

A normal adult can consume *C. botulinum* spores (e.g. raw vegetables) with no ill effects. However, if food is contaminated before preservation, the spores may germinate under anaerobic conditions producing highly poisonous toxin. *C. botulinum* spores survive standard cooking but the toxins are temperature sensitive and are inactivated by heating to 85°C for 5 min. The technique of industrial canning, where food is cooked at high temperatures to kill botulinum toxin and spores (retort canning), was developed specifically to kill *C. botulinum* spores. Destruction of spores requires food to be heated under pressure to 116°C for 15 min. Thus, home-canning food by boiling (100°C) without the use of a pressure cooker will not protect from botulism.

A case of food-borne botulism occurred in the Republic of Ireland in September 2006. Since the beginning of 2003, there have been a further four cases of food-borne botulism in the UK and the Republic of Ireland. Three of these five incidents involved Polish nationals, and were associated with the consumption of home prepared meat products originating from Poland.² The largest outbreak of food-borne botulism in the UK occurred in North West England and Wales in 1989. Twenty seven patients were identified. All but one of the patients were admitted to hospital, 12 were treated in Intensive Care and eight received positive pressure ventilation. One patient died from aspiration pneumonia. All had consumed hazelnut yoghurt. The illness was caused by type B toxin produced by bacteria growing in canned hazelnut yoghurt conserve that had

Key points

Wound botulism is increasing in the UK and occurs most frequently in injecting drug users. Food-borne botulism should be suspected in patients who may have consumed poorly preserved food.

The clinical syndrome produced by botulinum toxin is an afebrile, descending, symmetrical, flaccid paralysis of motor and autonomic nerves.

Respiratory failure can be rapid and may occur before other symptoms or signs become apparent.

It has been suggested that patients suspected of having botulism should be managed in a critical care environment.

Management is largely supportive together with administration of antitoxin.

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been inadequately heat treated and was used to flavour the yoghurt.³

In Alaska, botulism has been reported in natives who have consumed fermented beaver. Beaver is hunted in southwest Alaska, and certain parts may be fermented and eaten later. In an outbreak in 2001, the tail and paws had been wrapped in a paper rice sack and stored for up to 3 months in the entry of a patient's house. In traditional fermentation, food is kept in a grass-lined hole in the ground or a wooden barrel sunken into the ground for several weeks to months. However, since the 1970s, plastic or glass containers have been used and fermentation has been done above ground or indoors. The anaerobic condition of sealed containers makes production of botulinum toxin more likely.⁴

Wound botulism

Wound botulism follows infection of wounds caused by penetrating injuries. *C. botulinum* spores then germinate and produce toxin *in vivo*. The incidence of wound botulism appears to be increasing; it is the most common form of botulism in the UK. It was first reported in the UK among intravenous drug users in 2000. Between 2000 and 2005, 112 cases of suspected wound botulism were reported. All were amongst intravenous drug users. Injecting into muscle or under the skin (skin popping) increases the risk of wound botulism, as does the use of citric acid to dissolve heroin. High concentrations of citric acid can damage the muscle under the skin providing more favourable conditions for bacterial growth.⁵ Intravenous drug users 'skin pop' for a variety of reasons including personal choice, lack of veins, prolonged drug effect and to reduce the risk of overdose.

Intestinal colonization botulism

Intestinal colonization botulism in infants (infant botulism) results from ingestion of spores of *C. botulinum* which germinate, colonize the intestine and produce neurotoxin *in vivo*. It usually occurs in young infants but can occur in adults. There were six cases of infant botulism reported between 1978 and 2001. A route of infection was not identified in any of these except for a case report where *C. botulinum* type B was found from opened infant formula milk powder suggesting this was the source of exposure.⁶

C. botulinum as a bioweapon

Deliberate release could involve contamination of food and water supplies with toxin or bacteria, or airborne dissemination of toxin producing botulism after inhalation. Terrorists have already attempted to use botulinum toxin as a bioweapon. The Japanese cult Aum Shinrikyo dispersed aerosols at multiple sites in Tokyo and at US military installations in Japan on at least three occasions between 1990 and 1995. These attacks failed, apparently because of faulty microbiological technique, deficient aerosol-generating equipment, or internal sabotage. The terrorists obtained their *C. botulinum* from soil that they had collected in northern Japan.

Iraq admitted to weaponizing thousands of litres of botulinum toxin in warheads after the 1991 Gulf war.

In the United States, an investigational pentavalent (ABCDE) botulinum toxoid is distributed by the Centre for Disease Control for laboratory workers at high risk of exposure to botulinum toxin and by the military for protection of troops against attack. Mass immunization is not a practical option for reasons such as scarcity of the toxoid, rarity of natural disease and elimination of the potential benefits of medicinal botulinum toxin. Botulinum toxoid induces immunity over several months and so is ineffective post-exposure prophylaxis.⁷

Accidental botulism

Crystalline botulinum toxin type A was licensed in December 1989 by the Food and Drug Administration for treatment of certain spasmodic muscle disorders. Although the doses administered are sufficient to cause local muscle paralysis, the total dose is insufficient to cause severe systemic paralysis. There are a few reports of mild generalized weakness caused by therapeutic injection, although this is rare. It has been confirmed that distant effects on neuromuscular transmission and on autonomic function in patients injected with botulinum toxin for hemifacial spasm can occur.

Rare cases of inhalational botulism have been reported in individuals purifying the toxin. The symptoms are identical to food-borne botulism, although onset may be more rapid.

Clinical features

The onset of symptoms in naturally occurring cases of botulism is between 2 h and 8 days after ingestion, depending on the type and dose of toxin. There is a peak at 48 h. Patients may present to a wide range of specialties (e.g. neurology, ENT, ophthalmology, gastroenterology) because of the large spectrum of symptoms.

The key clinical syndrome produced by *C. botulinum* toxin is an afebrile, descending, symmetrical, flaccid paralysis of motor and autonomic nerves. Symptoms and signs are variable (Table 1); typically, patients present with sore throat and bulbar palsies including dysphonia, dysphagia, and diplopia. There is usually no loss of sensation, no loss of awareness, and no fever unless additional infection is present. Autonomic dysfunction may result in dry mouth and fixed or dilated pupils. Patients may also show signs of autonomic dysfunction of the cardiovascular, urinary, and gastrointestinal systems.

In cases of food-borne and intestinal colonization botulism, gastrointestinal symptoms such as nausea, vomiting, and diarrhoea may occur. Constipation often follows in food-borne botulism. Botulism can vary from a mild illness to fulminant disease that ends in death within 24 h. Although patients often present with a combination of symptoms and signs, it is important to be aware that respiratory failure may occur rapidly and before any other symptoms or signs become apparent.^{1,2} Deaths occurring within the first 2 weeks of botulism are most often due to failure to

Table 1 Symptoms and signs of botulism

Cranial nerves	Diplopia, blurred vision, photophobia, ptosis, dilated or fixed pupils, nystagmus, facial weakness, sore throat, dysphagia, dysarthria, dysphonia
Peripheries	Weakness in the neck and arms followed by respiratory muscles and muscles of the lower body, ataxia. Loss of deep tendon reflexes in severe disease
Autonomic system	Bladder distension, urinary incontinence/retention, paralytic ileus, dry mouth, postural hypotension, respiratory failure
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, abdominal pain (not with wound botulism)

recognize the severity of disease or from pulmonary or systemic infection. In adults, botulism results in pulmonary complications in 81% of patients, with ventilatory failure in one-third. For food-borne botulism, severity of disease seems to be associated with toxin type. Intubation is required for 67% of patients with type A botulism, 52% with type B botulism and 39% with type E botulism. In general, patients with wound botulism have a greater chance of requiring ventilation (two-thirds).

Differential diagnosis

Botulism is rarely seen in the UK and there are many other conditions with which it can be confused (Table 2). It is important to have a high index of suspicion of botulism when patients with typical symptoms and signs present, especially if they are intravenous drug users or have a history of consuming home preserved foods. A cluster of more than two cases with compatible symptoms is considered pathognomic because the conditions that most resemble botulism do not occur in outbreaks.⁸

Diagnosis

Confirmation of the clinical diagnosis is by the demonstration of botulinum toxin in the faeces, vomitus, serum or wound. Routine laboratory tests are not usually helpful, so specimens should be sent immediately to the reference laboratory. In the UK, this is the Food Safety Microbiology Laboratory in London, although occasionally samples are sent to Cardiff. The chances of detecting toxin diminish if collection is delayed. For food-borne botulism, toxin can be detected in the serum of more than 50% of cases if collected within 1 day of onset but in less than 25% after 3 days. Bacteria are present in faeces for a much longer duration and will be present in more than 40% of cases after 10 days.

Samples that should be taken are outlined in Table 3. Botulinum toxin cannot be absorbed through intact skin. However, toxin can be absorbed through mucosal surfaces, eyes, and non-intact skin. Standard precautions should be taken but there have been no cases of person-to-person transmission of botulism. All samples must be kept refrigerated after collection and should be sent in a cooked meat medium. The standard test is a bioassay involving intraperitoneal injection of toxin into mice and observation of the development of botulism-specific symptoms (the mouse lethality test). It takes 3 to 9 days to positively confirm the

presence of *C. botulinum*.² Other methods of detection include immunological assays, assays for botulinum neurotoxins based on their endopeptidase activity, and fibre-optic biosensors. Although the biosensors are not thought to be very sensitive, the principle offers potential for the rapid detection of botulinum neurotoxins.

In addition to identifying *C. botulinum* in specimens, neurophysiological assessment can be useful. The most consistent electrophysiological abnormality is a small compound muscle action potential in response to a supramaximal nerve stimulus.

Management

Specialist advice should be sought urgently from an infectious diseases physician or microbiologist. Management is largely supportive and, because of the risk of rapid respiratory failure, it has been suggested that patients suspected of having botulism should be cared for in a critical care setting.^{8,9}

Patients with pre-existing respiratory problems must be identified early as this can hasten respiratory failure. Respiratory rate, pulse oximetry, and arterial blood gas measurements should be monitored. However, it is recognized that desaturation or laboured breathing with an elevated respiratory rate may not develop until just before respiratory collapse. Forced vital capacity (FVC) should be measured serially and the trend used to assess the need for respiratory support (patients with FVC <15 ml/kg are likely to need respiratory support, patients with FVC <12 ml/kg are likely to need mechanical ventilation). If available, serial measurements of static inspiratory pressure ($P_{i_{max}}$) may also predict impending respiratory failure. A $P_{i_{max}}$ <15–20% predicted is useful in identifying patients who will ultimately require mechanical ventilation. In addition, there is evidence to suggest that these measurements should be repeated up to a minimum of 7 days after toxin ingestion in order to detect delayed ventilatory muscle strength.⁹

Elective intubation and mechanical ventilation should be undertaken in patients at risk of respiratory failure. This should be followed by standard intensive therapy including maintenance of adequate nutrition and hydration. Cardiac monitoring should be instituted to identify dysrhythmias that may require treatment.

A multidisciplinary approach is vital, as for any patient requiring intensive therapy. Weaning may take considerable time (sometimes months) and so a tracheostomy is often needed. It is important to be especially vigilant about patient comfort and positioning because botulism does not impair sensation. Care must be given in initiating oral feeding because patients are still prone to dysphagia and weakness of upper airway muscles may lead to aspiration. A soft diet may be required for several months. Physical therapy helps with early passive range of limb motion in the paralysed patient and later muscle strengthening exercises help recovery.

Specific therapy

The only specific therapy for botulism is antitoxin administration. Antitoxin is effective in reducing the severity of symptoms, if

Table 2 Diseases that may be confused with botulism

Condition	Clinical features	Diagnosis
Botulism	Acute bilateral symmetrical, descending paralysis. No sensory deficit, no fever, no lack of awareness	History of exposure. Identification of botulinum toxin in blood, pus, stool, vomitus, etc
Guillain-Barré syndrome (GBS)	History of febrile illness (campylobacter an identified cause), ascending paralysis, loss of sensation, pain, early loss of reflexes	Elevated CSF protein, nerve conduction studies, electromyogram (EMG)
Miller–Fisher variant of GBS	Similar to GBS but ocular muscles involved initially, descending paralysis, ataxia more marked than limb weakness	As above + anti GQ1b antibodies present in serum
Poliomyelitis	History of febrile illness, meningeal symptoms, asymmetric paralysis, no sensory involvement	Virus culture
Myasthenia Gravis	Fatigable muscle weakness, fluctuating proximal weakness	Tensilon test, serum acetylcholine receptor antibodies, nerve stimulation, muscle biopsy, presence of thymoma
Lambert-Eaton Myasthenic-myopathic syndrome (LEMS)	Non-metastatic manifestation of small cell carcinoma, proximal weakness which improves after repetitive muscle contraction, absent reflexes which also return after repetitive muscle contraction	EMG, repetitive stimulation, antibodies to calcium channel components in some cases
Tick bite	Ascending paralysis, loss of deep tendon reflexes, cranial nerve involvement rare	Travel to endemic area (USA, Australia), presence of tick parasite
Paralytic shellfish poisoning	Numbness of face and lips, paraesthesia, normal reflexes, respiratory failure	History of consumption of shellfish, incubation of <1 h
Viral encephalitis	Fever, altered mental state, asymmetrical weakness	Abnormal CSF, EEG, viral titres, e.g. Herpes simplex

Table 3 Samples to be taken and sent to the Food Safety Microbiology Laboratory²

Sample	Details
Food or water	Contact the local Consultant in Communicable Disease Control or the Health Protection Agency (HPA) on call duty doctor to arrange collection and transport
Serum	At least 10 ml, before antitoxin is administered
Pus or debrided tissue	As much as possible in a sterile container. If pus is not available then a swab of the lesion should be taken and placed immediately into transport medium for anaerobic culture
Faeces	At least 10 g in a sterile container. Rectal washout may be required
Vomitus, gastric washings or gut content	At least 10 g in a sterile container
Post-mortem specimens	Heart blood if not haemolysed. Specimens of faeces, gut contents or infected wounds may be useful

administered early in the course of the disease; however, it will not reverse established paralysis. It is vital to administer trivalent (A, B and E) antitoxin as soon as possible after a clinical diagnosis is made but preferably after appropriate specimens have been collected. Anaphylaxis, serum sickness and other hypersensitivity reactions may occur but the risk is low. However, before administration of antitoxin, skin testing should be performed to test for sensitivity to serum or antitoxin. The antitoxin can be repeated within 24 h if the patient continues to deteriorate. Antitoxin is held at different sites across the UK and can be accessed only by contacting the duty doctor at the Health Protection Agency.

Antitoxin is not recommended for infant botulism because of the lack of efficacy as a result of ongoing toxin release in the gut and the risk of adverse reactions. A recently published randomized, double-blind, placebo-controlled trial found that prompt treatment with human botulism immune globulin in cases of infant botulism was safe and effective in reducing the severity of illness and length of hospital stay.¹⁰

For cases of wound botulism, management consists of early wound debridement together with administration of antibiotics. Debridement of wounds should eradicate the infected lesion and stop toxin generation. However, it should ideally be performed

after the administration of antitoxin so that circulating toxin is neutralized. *C. botulinum* is sensitive to benzyl penicillin and metronidazole. Antimicrobial therapy is not recommended for cases of food-borne botulism.

Prognosis

Recovery from botulism is often prolonged and may require extensive rehabilitation. Ventilatory muscle recovery invariably occurs but it is slow and variable. Although ventilatory muscle strength is usually normal by 1 year, exercise capacity is often reduced. Patients may complain of marked fatigue, general weakness, dry mouth and shortness of breath that may persist for over a year, particularly if infected with type B botulinum toxin.

The overall mortality is ~7–10%. This is doubled for patients over the age of 60. The case-fatality rate for type A botulism is 10%, twice that of type B. Mortality rates of 60–70% have been quoted before the advent of mechanical ventilation.

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Please see multiple choice questions 18–20